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# Epidemiology Of Vestibular Schwannomas – Prospective 40-Year Data From An Unselected National Cohort

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**Objective:** Reports on the epidemiology of vestibular schwannoma (VS) indicate an increase in diagnosed cases, often based on selected materials over a limited period of time. This report presents prospective 40-year epidemiological data from an unselected national cohort of all patients diagnosed with a VS in Denmark since 1976.

**Study-design:** Data on gender, age, tumor localization and size registered during the period 1976–2015 were retrieved.

**Results:** 3637 new cases of VS were diagnosed during the 40-year period. The annual number of diagnosed VS increased from 14 in 1976 to 193 in 2015. Mean extrameatal tumor size decreased from 26mm in 1976 to 13.4mm in 2015. Large and giant tumors were more frequent during the first decades, whereas predominantly smaller tumors were diagnosed during the recent years. Median age at diagnosis increased gradually from 49.2 years in 1976 to 60 years in 2015.

**Conclusion:** Over the past 40 years, the incidence rate of vestibular schwannomas has increased steadily from 3 VS/million/year to 34 VS/million/year, primarily due to easier access to improved diagnostics and the finding of more tumors in older people. Concurrently, the diagnostic tumor size has decreased from 26mm to 7mm, and the age at diagnosis has increased from 49 to 60 years.

**Keywords:** acoustic neuroma, age, incidence, tumor localization, tumor size

## Introduction

All vestibular schwannomas diagnosed in Denmark have been managed at our tertiary referral center and registered prospectively in a database since 1976. Prior to this, data occur primarily in Danish neurosurgical publications.<sup>1</sup> Following the initiation of the database and the introduction of the translabyrinthine approach,<sup>2</sup> the recorded incidence rate of VS has been published successively, firstly by Tos and Thomsen and more lately by Stangerup et al.<sup>1,3–7</sup> In 2004, an increasing incidence rate of VS was reported, based on 1446 patients diagnosed during the period from 1976 to 2001<sup>1</sup> and in 2010 reported further increasing to a peak of 22.8 VS/million in 2004.<sup>6</sup> In 1976, the annual incidence rate was 3.1 VS/million, increasing to 19.4 VS/million in 2008, based on 2283 patients.<sup>6</sup>

Several other studies have also published data showing an increasing incidence rate of VS. Generally, incidences between 10 and 20 VS/million/year are reported, including data from America (Nestor et al<sup>8</sup>), Canada (Frohlich and Sutherland<sup>9</sup>), United Kingdom (Evans et al<sup>10</sup>) and locally in Denmark (Mirz et al<sup>11</sup>). Lately, American

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population-based registry studies have found similar incidences. Thus, Carlson et al<sup>12</sup> reported an incidence rate of 11 VS/million/year based on 8330 patients diagnosed during the period 2004–2011, and data on 23,729 patients registered in the Central Brain Tumor Registry of the United States during the period 2004–2010 showed an incidence rate of 10.9 million/year.<sup>13</sup> An earlier publication from the same registry reported an incidence rate of 6 VS/million/year.<sup>14</sup> From the Netherlands Cancer Registry, a publication from 2016 reported on 3663 patients diagnosed with VS during the period 2001 to 2012, showing an increase in incidence rate from 10.3 to 15.5 VS/million/year.<sup>15</sup> From Taiwan, a publication reported an increase in incidence rate from 26.6/million in 2001 to 37.2/million in 2012.<sup>16</sup> Lastly, in 2018, a publication from the USA (Minnesota) reported an increase in incidence rate from 15 VS/million/year in 1966 to 42 VS/million/year in 2016.<sup>17</sup>

The aim of this study is to report prospective 40-year epidemiological data from the Danish VS database, which contains the unselected, unbiased national cohort of all Danish patients diagnosed with a VS since 1976. Data on incidence rate, gender, age at diagnosis, tumor localization (purely intrameatal or extrameatal) and size registered during the period 1976–2015 are presented.

## Methods

Since 1976, data from all patients in Denmark with a sporadic/unilateral VS have been referred to our national treatment center, at which the patient data have been entered prospectively into the national VS database. The data are thus unselected and unbiased. Among other data, the tumor size, the tumor localization, the initial treatment strategy, gender and age of the patient at diagnosis were registered. The tumors were categorized as either intrameatal or extrameatal (intra- and extrameatal). The size of the extrameatal tumors was determined as the largest extrameatal diameter by linear measurements. This classification follows the Tokyo recommendations on reporting size of VS.<sup>18</sup>

This study reports the data on the annual incidence rate, the tumor localization and size at diagnosis, the age at diagnosis, and the relation between age and tumor size at diagnosis during the 40-year period from January 1, 1976 to January 1, 2016. A total of 3637 patients with sporadic/unilateral VS were registered and included in the database during this period, thus excluding patients diagnosed with Neurofibromatosis 2. The population in Denmark was 5.1 (5.065) million in 1976, increasing to 5.7 (5.707) million as of January 1, 2016.

**Table 1** Patients diagnosed with a VS in Denmark during the 40-year period 1976–2015

Patients	Tumor Localization			Total
	No Data	Intrameatal	Extrameatal	
Female	18	499	1287	1804
Male	15	596	1222	1833
Total	33	1095	2509	3637

## Results

### Gender And Tumor Localization At Diagnosis

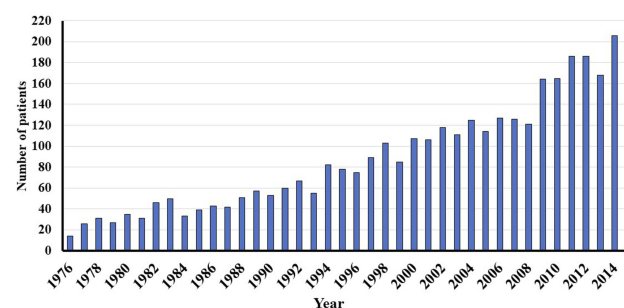
Of the 3637 diagnosed patients, 1804 were female and 1833 male. 1095 of the tumors had an intrameatal localization at diagnosis and 2509 were extrameatal. Localization data is missing for 33 patients (Table 1).

### Annual Incidence Rate

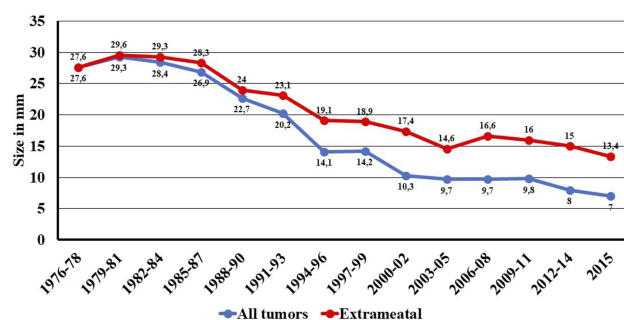
Since 1976, the annual number of diagnosed VS has increased almost linearly from 14 tumors in 1976 to 193 in 2015 (Figure 1), corresponding to an increase in incidence rate from 2.8 VS/million/year in 1976 to 33.8 VS/million/year in 2015.

### Diagnostic Tumor Size

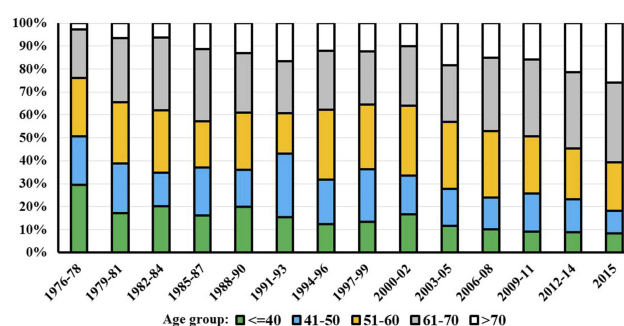
Diagnostic tumor size has decreased markedly, from a mean size of 27.6 mm in the period 1976 to 1978 to 7 mm in 2015 for all tumors (Figure 2). The mean extrameatal tumor size was 26 mm in 1976 decreasing to 13.4 mm in 2015. During the first three years, no intrameatal tumors were found, whereas such tumors constituted nearly half of the diagnosed tumors at the end of the 40-year period (Figure 3). The large and giant tumors constituted 40% of all tumors during the first years, only a few percent toward the end of the period (Figure 3).



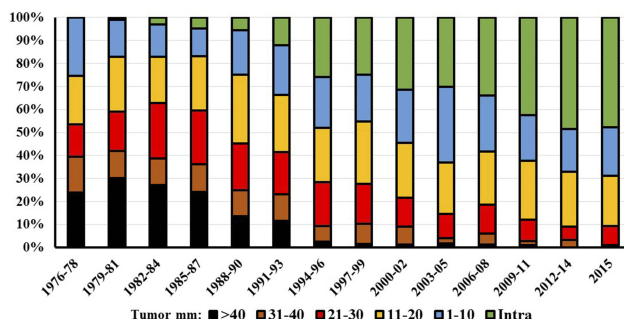
**Figure 1** Annual number of diagnosed vestibular schwannomas in Denmark during the 40-year period 1976–2015. The Danish population was 5.1 million in 1976 and 5.7 million in 2015.



**Figure 2** Mean tumor size at diagnosis over the 40-year period 1976–2015.



**Figure 5** Proportions of different age groups over the 40-year period 1976–2015.



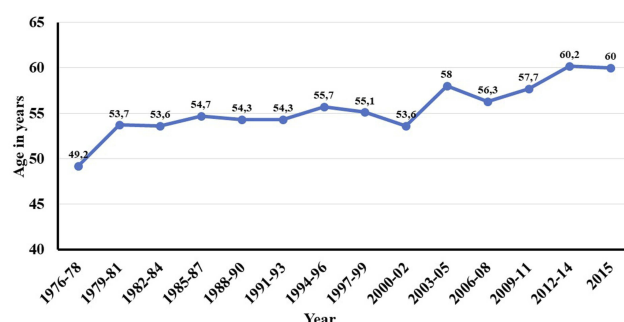
**Figure 3** Proportions of different tumor size groups (in mm) over the 40-year period 1976–2015.

## Patient Age At Diagnosis

The median age at diagnosis has increased slowly, from 49.2 years in 1976 to 60 years in 2015 (Figure 4). The age distribution at the time of diagnosis changed during the period, as seen in Figure 5. Initially, 51% of the VS patients were 50 years or younger, decreasing to 18% at the end of the period (Figure 5). In contrast, only 2.8% of the patients were older than 70 years in the beginning of the period, increasing to 26% at the end of the period.

## Tumor Size And Age At Diagnosis

Table 2 shows that the tumor size at diagnosis was larger in younger patients and smaller in older patients. Thus,



**Figure 4** Median patient age at diagnosis over the 40-year period 1976–2015.

patients below the age of 40 years had a mean tumor size of 19.7mm extrameatal, whereas patients above the age of 60 years had a mean tumor size of 11.1mm extrameatal.

## Discussion

This prospective study on 40-year epidemiological data from the unselected, unbiased national cohort of all Danish patients diagnosed with a VS since 1976 shows that the incidence rate of diagnosed tumors has been increasing steadily over the years, from 2.8 VS/million/year in 1976 to 33.8 VS/million/year in 2015. Improved diagnostics and increased availability of improved diagnostics are probably the main reasons for this increase, although an increased tumor occurrence cannot entirely be ruled out. The first MRI scanner in Denmark was functional in 1989 and by 2015, the number had increased to approximately 100. Increased awareness among patients and physicians is likely a contributing factor, as is an increasing number of older people, who in addition may be less and less likely to accept even a small loss of hearing, thus seeking a physician. More and more incidental findings due to an increased number of MRI scans, performed for reasons other than hearing loss, is also likely to be part of the explanation. On this basis, it is reasonable to assume that the incidence rate will increase continuously over the coming years.

Studies with higher incidence rates, ie 37,<sup>16</sup> 42<sup>17</sup> or 54<sup>19</sup> VS/million/year, have been published, from eg USA.

**Table 2** Mean tumor size (mm extrameatal  $\pm$ SD) related to age at diagnosis in patients diagnosed with a VS during the 40-year period 1976 – 2015

Age groups	Female	Male	All
≤40	20.8 $\pm$ 16.8	18.7 $\pm$ 16.5	19.7 $\pm$ 16.6
40–60	14.6 $\pm$ 13.6	13.1 $\pm$ 13.5	13.8 $\pm$ 13.6
>60	12.0 $\pm$ 12.7	10.0 $\pm$ 11.5	11.1 $\pm$ 12.2
All	14.2 $\pm$ 13.9	12.5 $\pm$ 13.4	13.3 $\pm$ 13.7

A number of biases may be contributing, including easier access to health care in more affluent parts of the world or less strict criteria of indication to perform MRI, based on eg tinnitus, a smaller degree of hearing loss, or any other symptom or finding that may lead to MRI of the head and thus an incidental tumor finding. The two reports from America both have populations with easier access to the healthcare system (ie Mayo Clinic, Rochester) or belong to a very affluent part of the population (ie Beverly Hills, California). Denmark has a state-funded healthcare system financed through general taxation and every citizen can consult an ENT specialist (and have an MRI if indicated) free of charge and without a referral. Despite this, even in a very equal and homogeneous population such as the Danish, a study on socio-demographic factors demonstrated lower incidence rates in remote parts of the country which is relatively small, but the same diagnostic age and tumor size across the country.<sup>20</sup> Thus, socio-economic and socio-demographic factors can explain some of the differences in reported incidence rates but are unlikely to directly explain the degree of occurrence of higher incidences reported by other centers.

Over the four decades, diagnostic tumor size has decreased steadily, from 28 mm extrameatal in the late seventies to 7 mm extrameatal in 2015, which is in agreement with an increased incidence rate associated with improved diagnostic tools (contemporary imaging can detect very small tumors, which were undetectable before the introduction of MRI). It is also in agreement with the assumption that patients seek medical consultation based on fewer symptoms. Thus, tumors are found at an earlier stage of development, when the tumor size is smaller.

Tumor aggressiveness appears to be inversely related to age, as in general, large tumors are found in young patients, small tumors in older patients. This is corroborated, but remain unexplained, by studies on the natural history of tumor growth, as small intrameatal tumors (usually found in older patients) are less likely to grow compared to larger, extrameatal tumors (which are usually found in younger patients).<sup>7</sup> Studies on tumor gene expression have demonstrated the association between growth and expression of certain genes and activation of specific molecular pathways but have not accounted for age-related tumor aggressiveness.<sup>21</sup>

Age at tumor diagnosis is steadily increasing, from 49.2 years of age to currently 60 years of age. Demography in Denmark, and in general, is shifting progressively towards older people, which may also be a major reason for the

increasing age at diagnosis. In addition, older people are more likely to seek a physician and have an MRI performed due to higher morbidity in general, but certainly also due to the occurrence of age-related hearing loss. Finally, in continuation of the discussion on improved diagnostics, the small tumors within the older patient group were simply not found previously, before the introduction of MRI.

The etiopathogenesis of sporadic/unilateral VS is unaccounted for and several studies have investigated risk factors and associations with VS. No obvious risk factors have been found regarding age and gender. Viral infection has been indicated,<sup>21–23</sup> which is in line with the fact that these tumors have been occurring for centuries. In continuation of this, the theory of inflammation as a cause of VS has given rise to studies and reported association to chickenpox,<sup>24</sup> hay fever<sup>25</sup> and conflicting studies of the protective effects of aspirin/NSAID.<sup>26–29</sup> Furthermore, a few studies have reported tobacco use (not snuff tobacco) being inversely related to VS occurrence, although this is poorly understood.<sup>25,30–33</sup> None of the studies are prospective, randomized or blinded but mostly case–control studies. Of importance, no association has been found between occupation, traffic/loud noise nor the use of mobile phones and tumor occurrence.<sup>34–37</sup> Lastly, exposure to radiation is known to cause neoplasms including intracranial.<sup>38–41</sup>

## Conclusion

Over the past 40 years, the incidence rate of vestibular schwannomas has increased steadily from approximately 3 VS/million/year to 34 VS/million/year, primarily due to continuously easier access to improved diagnostics and the finding of more tumors in older people. Concurrently, the diagnostic tumor size has decreased from 26 mm to 7 mm, and the age at diagnosis has increased from approximately 49 to 60 years of age.

## Data Sharing Statement

The data is accessible in the national vestibular schwannoma database and available for the author group.

## Acknowledgments

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## Disclosure

The authors report no conflicts of interest in this work.



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